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(54) Title: NUCLEOSIDE METABOLISM INHIBITORS

(57) Abstract: The present invention provides a compound of formula (I), wherein: A is selected from N, CH and CR, where R is selected from halogen, optionally substituted alkyl, aralkyl and aryl, OH, NH₂, NHR¹, NR¹R² and SR³, where R¹, R² and R³ are each optionally substituted alkyl, aralkyl or aryl groups; B is selected from OH, NH₂, NHR⁴, H and halogen, where R⁴ is an optionally substituted alkyl, aralkyl or aryl group; D is selected from OH, NH₂, NHR⁵, H, halogen and SCH₃, where R⁵ is an optionally substituted alkyl, aralkyl or aryl group; X and Y are independently selected from H, OH and halogen, with the proviso that when one of X and Y is hydroxy or halogen, the other is hydrogen; Z is OH, or, when X is hydroxy, Z is selected from hydrogen, halogen, hydroxy, SQ and OQ, where Q is an optionally substituted alkyl, aralkyl or aryl group; and W is OH or H, with the proviso that when W is OH, then A is CR where R is as defined above; or a tautomer thereof; or a pharmaceutically acceptable salt thereof; or an ester thereof; or a prodrug thereof. The invention also provides a pharmaceutical composition comprising a compound of formula (I), as well as methods of treatment using a compound of formula (I). The invention further provides methods of preparing compounds of formula (I).

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NUCLEOSIDE METABOLISM INHIBITORS

5 TECHNICAL FIELD

This invention relates to certain nucleoside analogues, pharmaceutical compositions containing the compounds and processes for preparing the compounds.

10

BACKGROUND OF THE INVENTION

Purine nucleoside phosphorylase (PNP) catalyses the phosphorolytic cleavage of ribo- and deoxyribonucleosides, for example, those of guanine and hypoxanthine to give the corresponding sugar-1-phosphate and guanine, hypoxanthine, or other purine bases.

15

Humans deficient in purine nucleoside phosphorylase (PNP) suffer a specific T-cell immunodeficiency due to an accumulation of dGTP and its toxicity to stimulated T lymphocytes. Because of this, inhibitors against PNP are immunosuppressive, and are active against T-cell malignancies. Clinical trials are now in progress using 9-(3-pyridylmethyl)-9-deazaguanine in topical form against psoriasis and in oral form for T-cell lymphoma and immunosuppression (BioCryst Pharmaceuticals, Inc). The compound has an IC₅₀ of 35 nM for the enzyme. In animal studies, a 50 mg/kg oral dose is required for activity in a contact sensitivity ear swelling assay in mice. For human doses, this would mean approximately 3.5 grams for a 70 kg human. With this inhibitor, PNP is difficult to inhibit due to the relatively high activity of the enzyme in blood and mammalian tissues.

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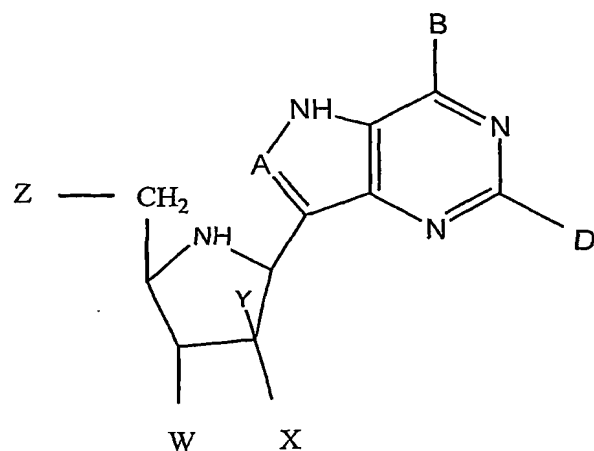
Nucleoside and deoxynucleoside hydrolases catalyse the hydrolysis of nucleosides and deoxynucleosides. These enzymes are not found in mammals but are required for nucleoside salvage in some protozoan parasites. Purine phosphoribosyltransferases (PPRT) catalyze the transfer of purine bases to 5-phospho- α -D-ribose-1-pyrophosphate to form purine nucleotide 5'-phosphates. Protozoan and other parasites contain PPRT which are involved in essential purine salvage pathways. Malignant tissues also contain PPRT. Some protozoan parasites contain purine nucleoside phosphorylases which also function in purine salvage pathways. Inhibitors of nucleoside hydrolases, purine nucleoside phosphorylases and PPRT can be expected to interfere with the metabolism of parasites and therefore be usefully employed against protozoan parasites. Inhibitors of PNP and PPRT can be expected to interfere with purine metabolism in malignant tissues and therefore be usefully employed against malignant tissues.

The applicants' PCT International Patent publication WO 99/19338 describes compounds which are potent inhibitors of PNP, PPRT and/or nucleoside hydrolases.

It is an object of the present invention to provide further compounds which are effective inhibitors of PNP, PPRT and/or nucleoside hydrolases, or at least to provide the public with a useful choice.

SUMMARY OF THE INVENTION

Accordingly, in a first aspect, the present invention provides a compound of the formula:



(II)

wherein:

5 A is selected from N, CH and CR, where R is selected from halogen, optionally substituted alkyl, aralkyl and aryl, OH, NH₂, NHR¹, NR¹R² and SR³, where R¹, R² and R³ are each optionally substituted alkyl, aralkyl or aryl groups;

10 B is selected from OH, NH₂, NHR⁴, H and halogen, where R⁴ is an optionally substituted alkyl, aralkyl or aryl group;

D is selected from OH, NH₂, NHR⁵, H, halogen and SCH₃, where R⁵ is an optionally substituted alkyl, aralkyl or aryl group;

15 X and Y are independently selected from H, OH and halogen, with the proviso that when one of X and Y is hydroxy or halogen, the other is hydrogen;

20 Z is OH, or, when X is hydroxy, Z is selected from hydrogen, halogen, hydroxy, SQ and OQ, where Q is an optionally substituted alkyl, aralkyl or aryl group; and

W is OH or H, with the proviso that when W is OH, then A is CR where R is as defined above;

or a tautomer thereof; or a pharmaceutically acceptable salt thereof; or an ester thereof; or a prodrug thereof.

Preferably when B is NHR^4 and/or D is NHR^5 , then R^4 and/or R^5 are $\text{C}^1\text{-C}^4$ alkyl.

Preferably when one or more halogens are present they are chosen from chlorine and fluorine.

Preferably when Z is SQ or OQ, Q is $\text{C}_1\text{-C}_5$ alkyl or phenyl.

Preferably D is H, or when D is other than H, B is OH.

More preferably, B is OH, D is H, OH or NH_2 , X is OH or H, Y is H, most preferably with Z as OH, H, or methylthio, especially OH.

In certain preferred embodiments W is OH, Y is H, X is OH, and A is CR where R is methyl or halogen, preferably fluorine.

In other preferred embodiments, W is H, Y is H, X is OH and A is CH.

It will be appreciated that the representation of a compound of formula (I) wherein B and/or D is a hydroxy group used herein is of the enol-type tautomeric form of a corresponding amide, and this will largely exist in the amide form. The use of the enol-type tautomeric representation is simply to allow fewer structural formulae to represent the compounds of the invention.

According to another aspect of the invention, there is provided a pharmaceutical composition comprising a pharmaceutically effective amount of a compound of the formula (I) as defined above.

5 In another aspect, the invention provides methods for treatment of diseases or conditions in which it is desirable to decrease the level of T lymphocyte activity, the method comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound as defined above.

10 In a further aspect, the invention provides methods for treatment and/or prophylaxis of parasitic infections, particularly those caused by protozoan parasites, the method comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound as defined above.

15 In further aspects, the invention provides methods of preparing compounds of formula (I) as defined above.

20 While the invention is broadly as defined above, it is not limited thereto and also includes embodiments of which the following description provides examples.

DESCRIPTION OF THE INVENTION

25 This invention provides novel compounds of the formula (I) as defined above, which are potent inhibitors of purine nucleoside phosphorylase, nucleoside hydrolases and/or phosphoribosyltransferases.

30 The compounds of the invention are therefore expected to have clinical utility in treating conditions in which it is desirable to decrease the level of T lymphocyte activity, such as T-cell malignancies and autoimmune diseases,

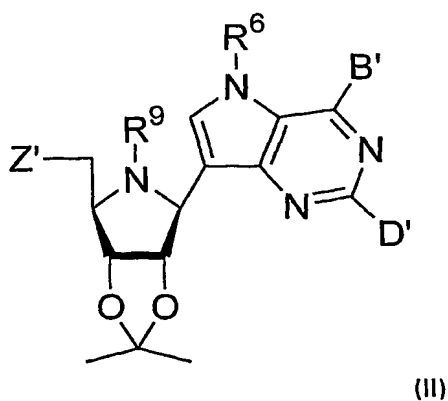
including arthritis and lupus. The invention also contemplates use of the compounds for immunosuppression for organ transplantation and for inflammatory disorders. The compounds of the invention are also expected to have utility in methods of treatment and/or prophylaxis of parasitic infections, particularly those caused by protozoan parasites, such as *Giardia*, *Trichomonas*, *Leishmania*, *Trypanosoma*, *Crithidia*, *Herpetomonas*, *Leptomonas*, *Histomonas*, *Eimeria*, *Isopora* and *Plasmodium*.

The compounds of formula (I) of the invention may be prepared by the methods described below:

Method A

This method may be used to prepare compounds of the formula (I) in which A is CR, where R is as defined above; ie compounds which are substituted at C-8 of the 9-deazapurine moiety.

The method comprises reacting a compound of formula (II)



wherein R^9 is an alkoxy carbonyl or aralkoxy carbonyl group, Z' is a hydrogen or halogen atom, a group of formula SQ or OQ, or a trialkylsilyloxy, alkyl diarylsilyloxy or optionally substituted triarylmethoxy group and Q is an

optionally substituted alkyl, aralkyl or aryl group, and R^6 is an N-protecting group, B' and D' are independently selected from H, OR^7 and $N(R^8)_2$, and R^7 and R^8 are O- and N- protecting groups respectively;

- 5 (i) with a strong base capable of deprotonation at C-8 of the 9-deazapurine moiety; then
- (ii) with an electrophile; and
- (iii) O- and N-deprotecting the product by acid-, alkali- or fluoride ion-catalyzed hydrolysis or alcoholysis or catalytic hydrogenolysis as required for
- 10 the O- and N-protecting groups in use.

Suitable strong bases are butyllithium and *tert*-butyllithium. Suitable electrophiles are N-fluorosulfomidobenzene, alkyl halides such as methyl iodide, aldehydes such as acetaldehyde, or formylating agents such as

15 dimethylformamide.

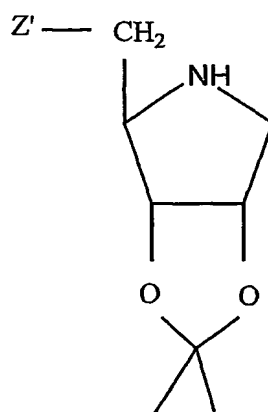
A compound of formula (II) can be prepared as described in the applicants' PCT International patent application PCT/NZ00/00048 entitled "Processes for preparing inhibitors of nucleoside metabolism" and filed on 7 April 2000,

20 by N-protection of the product obtained by the coupling of a 1,N-dehydro-1,4-dideoxy-1,4-imino-D ribitol derivative with a protected 7-halogeno-deazapurine derivative (therein described as pyrrolopyrimidine derivatives).

More specifically, a compound of the formula (II) can be prepared by the

25 following process:

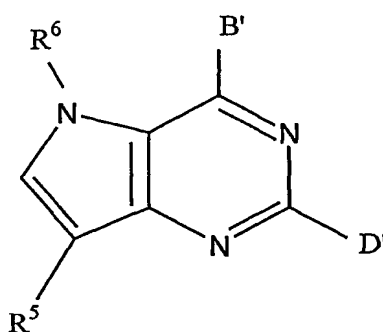
- (a) reacting a compound of the formula (IV)



(IV)

wherein Z' is a hydrogen or halogen atom, a group of formula SQ or OQ, or a trialkylsilyloxy, alkyldiarylsilyloxy or optionally substituted triarylmethoxy group and Q is an optionally substituted alkyl, aralkyl or aryl group, sequentially with a halogenating agent and a sterically hindered base to form an imine;

(b) condensing the imine thus prepared with an anion produced by abstraction of the bromine or iodine atom from a compound of formula (XIX): wherein R⁵ is a bromine or iodine atom, R⁶ is an N-protecting group, B' and



(XIX)

D' are independently selected from H, OR⁷ and N(R⁸)₂, and R⁷ and R⁸ are O- and N- protecting groups respectively, to produce a 1-C-(pyrrolo[3,2-*d*]pyrimidin-7-yl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribose

derivative of formula (II) as defined above, but in which R⁹ is a hydrogen atom; and

(c) converting the compound to a compound of formula (II) in which R⁹ is alkoxy carbonyl or aralkoxy carbonyl.

The compounds of formula (II) where R⁹ is a hydrogen atom can be converted into compounds of formula (II) where R⁹ is an alkoxy carbonyl or aralkoxy carbonyl group by N-protecting with an appropriate compound containing the desired alkoxy carbonyl or aralkoxy carbonyl moiety. A suitable N-protecting group is the *tert*-butoxy carbonyl group, which can be introduced by the use of *tert*-butyl dicarbonate, for example in methylene chloride followed by chromatography.

The halogenating agent used in step (a) above may conveniently be N-chlorosuccinimide; and the hindered base used in step (a) may conveniently be lithium tetramethyl piperidide.

In step (b) above the bromide or iodine atom may conveniently be abstracted from the compound of formula (XIX) using butyllithium or magnesium.

The N-protecting group R⁶ in the compound of formula (XIX) may conveniently be an alkoxymethyl group (such as benzyloxymethyl), a silyl group (such as *tert*-butyldimethylsilyl) or an arylmethyl group (such as benzyl). The O-protecting group R⁷ may conveniently be an alkyl or arylmethyl group (such as methyl, *tert*-butyl or benzyl), and each N-protecting group R⁸ may conveniently be independently an arylmethyl group (such as benzyl or 4-methoxybenzyl), or the two R⁸ groups together may form the 2,4-hexadien-2,5-yl group.

The compounds of formula (XIX) defined above may be prepared by known methods. Compounds of the formula (IV) defined above may also be

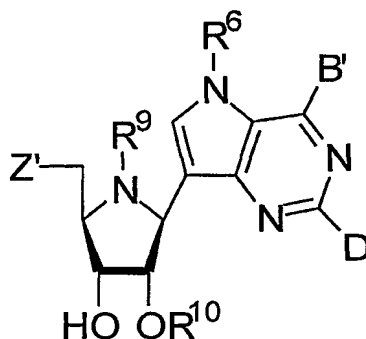
prepared by known methods, for example as described in WO 99/19338 and the references cited therein.

Method B

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This method may be used to prepare compounds of the formula (I) in which W is H (ie 3'-deoxy compounds of formula (I)).

This method comprises reacting a compound of formula (III)



10

(III)

wherein R^9 is an alkoxycarbonyl or aralkyloxycarbonyl group, Z' is a hydrogen or halogen atom, a group of formula SQ or OQ, or a trialkylsilyloxy, alkyldiarylsilyloxy or optionally substituted triarylmethoxy group and Q is an optionally substituted alkyl, aralkyl or aryl group, and R^6 is an N-protecting group, B' and D' are independently selected from H, OR^7 and $N(R^8)_2$, R^7 and R^8 are O- and N-protecting groups, respectively, and R^{10} is an O-protecting group;

20

- (i) with a thiocarbonylating agent; then
- (ii) with a radical reducing agent; and

(iii) O- and N-deprotecting the product by acid-, alkali- or fluoride ion-catalyzed hydrolysis or alcoholysis or catalytic hydrogenolysis as required for the O- and N-protecting groups in use.

5 Together, steps (i) and (ii) are known as the Barton deoxygenation sequence. Suitable thiocarbonylating agents are thiocarbonyl diimidazole, phenoxythiocarbonyl chloride, or the combination of a base, carbon disulfide and methyl iodide. Suitable radical reducing agents are tributyltin hydride and lauroyl peroxide.

10

A compound of formula (III) can be prepared from a compound of formula (II) above by:

- 15 (i) removal of the 2,3-O-isopropylidene group by acid-catalyzed hydrolysis;
(ii) N-protection;
(iii) selective reprotection of the 5'-hydroxy-group if necessary; and
(iv) selective reprotection of the 2'-hydroxy-group.

20 Step (i) can conveniently be conducted by treatment with trifluoroacetic acid in an aqueous organic solvent under reflux. Certain 5'-O-protecting groups, such as a *tert*-butyldimethyl silyl group, may simultaneously be removed under these conditions, necessitating reprotection in step (iii). Reprotection can conveniently be achieved by treatment with a reagent capable of
25 effecting selective protection of a primary hydroxy group in the presence of a secondary hydroxy group, such as trityl chloride and base.

A suitable N-protecting group is the *tert*-butoxycarbonyl group, which can be introduced by the use of *tert*-butyl dicarbonate in step (ii).

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Selective protection of the 2'-hydroxy-group can be effected by activation of the 2',3'-diol as a stannylidene acetal, e.g. by reaction with dibutyltin oxide,

and fluoride ion catalyzed reaction with a reagent capable of delivering an O-protecting group, such as 4-methoxybenzyl chloride and base.

Three preferred compounds of the present invention are:

5

(1S)-1-(9-deaza-8-fluorohypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribose;

(1S)-1-(9-deaza-8-methylhypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribose; and

10

(1S)-1-(9-deazahypoxanthin-9-yl)-1,3,4-trideoxy-1,4-imino-D-ribose.

These compounds may conveniently be prepared as their hydrochloride salts.

15

The compounds of the invention are useful both in free base form and in the form of salts. The term "pharmaceutically acceptable salts" is intended to apply to non-toxic salts derived from inorganic or organic acids, including for example salts derived from the following acids - hydrochloric, sulfuric, phosphonic, acetic, lactic, fumaric, succinic, tartaric, gluconic, citric, methanesulphonic and p-toluenesulphonic acids.

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The dosage of the compound to be administered can vary widely according to the nature of the patient and the disorder being treated. However, typically the dosage for an adult human will be in the range of 0.1-1000 mg. The compounds can be administered in combination with one or more conventional pharmaceutical carriers or excipients and may be administered orally, by injection or topically.

The invention will be described in more detail with reference to the following non-limiting examples.

EXAMPLES

Example 1

5 Preparation of 5-O-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-ribose.

5-O-*tert*-Butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-ribose was treated with NBS and then lithium tetramethylpiperide as described previously (Evans, G.B.; Furneaux, R.H.; Gainsford, G.J.; Schramm, V.L.; Tyler, P.C. *Tetrahedron* 2000, 56, 3053). The cold reaction mixture was partitioned between petroleum ether and water and processed normally. Chromatography of the residue (EtOAc/Petroleum ether/Triethylamine 100/200/1 v/v/v) afforded 5-O-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-ribose in ~ 80 % yield which was used directly.

Example 2

20 Preparation of 7-N-benzoyloxymethyl-9-bromo-9-deaza-6-O-ethylhypoxanthine.

Sodium hydride (1.88 g, 60 % dispersion, 47 mmol) was added to a stirred suspension of 6-chloro-9-deazapurine (K. Imai, *Chem. Pharm. Bull.* 1964, 12, 1030) (5.19 g, 33.8 mmol) in THF (80 mL) and the resulting mixture was stirred in an ice bath while benzyl chloromethyl ether (6 mL, 43 mmol) was added slowly. The mixture was then stirred at room temperature for 1 h. Methanol (20 mL) and sodium hydride (1.6g, 60 %, 40 mmol) were added carefully and then after 1h NBS was added portion-wise until t.l.c. analysis indicated the initial material was replaced by a less polar product. The solution was washed with water (x2), and processed normally. Chromatography afforded 7-N-benzoyloxymethyl-9-bromo-9-deaza-6-O-methylhypoxanthine (6.83 g, 19.6 mmol) as a solid. Recrystallized from

ethanol it had m.p. 98-99 °C; ^1H NMR δ 8.60 (s, 1H), 7.44 (s, 1H), 7.35-7.21 (m, 5H), 5.71 (s, 2H), 4.48 (s, 2H), 4.11 (s, 3H); ^{13}C NMR δ 156.8 (C), 151.4 (CH), 148.8, 136.9 (C), 131.9, 128.9, 128.5, 128.0 (CH), 116.0, 92.8 (C), 77.6, 70.8 (CH₂), 54.2 (CH₃). Anal. calc. for C₁₅H₁₄BrN₃O₂: C, 51.74; H, 4.05; Br, 22.95; N, 12.07. Found: C, 51.97; H, 3.91; Br, 23.19; N, 12.28.

Example 3

10 Preparation of 7-*N*-benzyloxymethyl-9-bromo-6-*O*-*tert*-butyl-9-deazahypoxanthine.

Sodium hydride (60 % dispersion, ~1.5 g) was added slowly to a stirred suspension of 6-chloro-9-deazapurine (5.0 g) and chloromethyl benzyl ether (6 mL) in dry THF (100 mL) in an ice bath until effervescence had ceased. Then *tert*-butyl alcohol (20 mL), DMF (20 mL) and more sodium hydride (60 %, 1.5 g) were added, the cooling bath was removed and the mixture was stirred at rt for 24 h. Chloroform (200 mL) was added and the mixture was washed with water (x2) and processed normally. A solution of the crude residue in chloroform (50 mL) was stirred in an ice bath while NBS (~5 g) was added portion-wise until TLC indicated the reaction was complete. Chromatography then afforded 7-*N*-benzyloxymethyl-9-bromo-6-*O*-*tert*-butyl-9-deazahypoxanthine as a pale yellow solid (5.8 g). ^1H NMR (CDCl₃) δ 8.55 (1H, s), 7.41 (1H, s), 7.34-7.20 (5H, m), 5.73 (2H, s), 4.48 (2H, s), 1.69 (9H, s); ^{13}C NMR (CDCl₃) δ 156.3 (C), 151.1 (CH), 148.7, 137.1 (C), 131.4, 128.9, 128.4, 127.8 (CH), 117.0, 92.6, 84.0 (C), 77.6, 70.5 (CH₂), 29.0 (CH₃).

Example 4

Preparation of 1-(S)-(7-N-benzyloxymethyl-6-O-*tert*-butyl-9-deazahypoxanthin-9-yl)-N-*tert*-butoxycarbonyl-5-O-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-ribitol.

A solution of the product from example 3 (2.7 g) in anisole (20 mL) and ether (40 mL) was cooled to - 60 °C and butyl lithium (2.9 mL, 2.4 M in hexanes) was added. Then a solution of the product from example 1 (1.6 g) in ether (5 mL) was added. The solution was allowed to warm slowly to 10 °C and then washed with water, dried and concentrated to dryness. Chromatography afforded the product mixed with the debrominated deazahypoxanthine derivative. This mixture was dissolved in dichloromethane (20 mL) and di *tert*-butyl-dicarbonate (1.06 g) was added. After 1 h the solution was concentrated and chromatography afforded 1-(S)-(7-N-benzyloxymethyl-6-O-*tert*-butyl-9-deazahypoxanthin-9-yl)-N-*tert*-butoxycarbonyl-5-O-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-ribitol (2.17 g).

Example 5

Preparation of 1-(S)-(7-N-benzyloxymethyl-9-deaza-6-O-methylhypoxanthin-9-yl)-N-*tert*-butoxycarbonyl-5-O-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-ribitol.

A solution of the product from example 2 (16.0 g, 46 mmol) in anisole (120 mL) and ether (200 mL) was treated with butyl lithium at - 35 ° C and then the product from example 1 as described above in example 4. The crude product in methylene chloride (100 mL) was treated with di-*tert*-butyl dicarbonate (8.0 g, 36 mmol) and the solution was stirred for 1 h, then concentrated to dryness. Chromatography of the residue afforded 1-(S)-(7-N-benzyloxymethyl-9-deaza-6-O-methylhypoxanthin-9-yl)-N-*tert*-

butoxycarbonyl-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (18.8 g, 28.7 mmol) as a syrup. ¹H NMR (C₆D₆ at 70 °C) δ 8.67 (1H, s), 7.48 (1H, br s), 7.09 (5H, m), 5.78 (1H, br s), 5.67 (1H, s), 5.44 (1H, br s), 5.25 (2H, s), 4.54 (1H, br s), 4.23 (2H, s), 4.09 (1H, t, *J* = 9.7 Hz), 3.97 (1H, br s), 3.77 (3H, s), 1.57 (3H, s), 1.42 (9H, s), 1.33 (3H, s), 0.97 (9H, s), 0.11 (6H, s); ¹³C NMR (C₆D₆ at 70 °C) δ 156.7, 154.8 (C), 150.4 (CH), 149.4, 137.9, 133.8, 116.4, 111.9 (C), 84.6, 84.0 (CH), 79.6 (C), 77.3, 70.4 (CH₂), 67.7 (CH), 63.4 (CH₂), 61.9 (CH), 53.0 (CH₃), 28.7, 27.9, 26.3, 25.8 (CH₃), 18.6 (C), -4.9, -5.0 (CH₃). Some aromatic signals were obscured by the solvent. HRMS (MH⁺) calc. for C₃₄H₅₁N₄O₇Si: 655.3527. Found: 655.3553.

Example 6

Preparation of (1*S*)-1-(9-deaza-8-fluorohypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride.

A solution of the product from example 4 (1.25 g) in THF (30 mL) was cooled to - 70 °C and butyl lithium (1.5 mL, 2.4 M in hexanes) was added slowly. After 10 mins *N*-fluorobenzenesulfonimide (1.42 g) was added to the red/brown solution. After 20 mins the solution was partitioned between water and chloroform. The organic phase was processed normally and chromatography afforded 1-(*S*)-(7-*N*-benzyloxymethyl-6-*O*-*tert*-butyl-9-deaza-8-fluorohypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-5-*O*-*tert*-butyldimethylsilyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (0.67 g). A solution of 0.2 g of this material in THF (5 mL) and methanol (5 mL) was stirred with tetrabutylammonium fluoride (5 mL, 1 M in THF) for 18 h. The solution was concentrated and a solution of the residue in toluene (15 mL) was washed with water (x2), dried and concentrated to dryness. The residue in ethanol (10 mL) was stirred under hydrogen in the presence of 10 % Pd/C (0.2 g) for 18 h. The solids and solvent were removed and chromatography afforded two products, one with and one without the 6-*O*-*tert*-butyl residue on the

hypoxanthine moiety. These were combined in methanol (4 mL) and 2M aq HCl (4 mL) was added. After 2 h the solution was concentrated to dryness and the residue was recrystallised from aq acetone to give (1*S*)-1-(9-deaza-8-fluorohypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride (0.043 g). ¹H NMR (D₂O) δ 8.04 (1H, s), 4.97-4.88 (2H, m), 4.48 (1H, t, *J* = 4.1 Hz), 3.93 (2H, m), 3.89 (1H, dd, *J* = 4.6, 9.0 Hz). Anal. calc. for C₁₁H₁₄ClFN₄O₄: requires C, 41.20; H, 4.40; Cl, 11.05; N, 17.47. Found: C, 41.01; H, 4.37; Cl, 11.11; N, 17.17.

Example 7

Preparation of (1*S*)-1-(9-deaza-8-methylhypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride.

A solution of the product from example 5 (0.29 g) in THF (7 mL) was cooled to -70 °C and butyl lithium (0.4 mL, 2.4 M in hexanes) was added slowly. After 10 mins methyl iodide (0.25 mL) was added and 10 mins later the solution was partitioned between chloroform and water and the organic layer was processed normally followed by chromatography affording the 8-C-methyl product (0.164 g). This material in ethanol (5 mL) was stirred under hydrogen with 10 % Pd/C (0.1 g) for 3 days. Removal of the solids and solvent and chromatography afforded 1-(*S*)-(9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (0.089 g). A solution of this material in methanol (3 mL) and conc aq HCl (3 mL) was heated under reflux for 2 h and then concentrated to dryness to give (1*S*)-1-(9-deaza-8-methylhypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride (0.061 g) as a white solid. ¹H NMR (D₂O) δ 8.46 (1H, s), 4.96 (1H, dd, *J* = 9.4, 4.6 Hz), 4.89 (1H, d, *J* = 9.5 Hz), 4.51 (1H, m), 4.07 (2H, m), 3.96 (1H, m), 2.54 (3H, s). Anal. calc. for C₁₂H₁₇ClN₄O₄: C, 45.50; H, 5.41; Cl, 11.19; N, 17.69. Found: C, 45.38; H, 5.41; Cl, 11.50; N, 17.80.

Example 8**Preparation of 1-(S)-(7-N-benzyloxymethyl-9-deaza-6-O-methylhypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-ribitol.**

5

A solution of the product from example 2 (4.4 g, 12.6 mmol) in anisole (60 mL) and ether (100 mL) was treated with butyl lithium and then the product from example 1 (2.4 g, 8.4 mmol) as described above in example 4, except that it was not treated with di *tert*-butyl-dicarbonate. Tetrabutylammonium fluoride (15 mL, 1 M in THF) was added to a solution of the crude product in THF (20 mL) and after 1 h toluene (100 mL) was added and the solution was washed with water (x2) and then processed normally. Chromatography afforded syrupy 1-(S)-(7-N-benzyloxymethyl-9-deaza-6-O-methylhypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-2,3-O-isopropylidene-D-ribitol (2.27 g, 5.16 mmol). ¹H NMR (CDCl₃) δ 8.51 (s, 1H), 7.38 (s, 1H), 7.35-7.22 (m, 5H), 5.73 (d, *J* = 10.6 Hz, 1H), 5.65 (d, *J* = 10.6 Hz, 1H), 4.89 (t, *J* = 5.7 Hz, 1H), 4.77 (dd, *J* = 6.0, 2.1 Hz, 1H), 4.50 (d, *J* = 5.5 Hz, 1H), 4.48 (s, 2H), 4.09 (s, 3H), 3.74 (s, 1H), 3.73 (s, 1H), 3.64 (dd, *J* = 5.3, 2.9 Hz, 1H), 1.61 (s, 3H), 1.36 (s, 3H); ¹³C NMR δ 156.8 (C), 150.1 (CH), 149.2, 137.3 (C), 130.9, 128.8, 128.4, 128.0 (CH), 118.3, 117.1, 113.1 (C), 86.1, 83.9 (CH), 77.3, 70.6 (CH₂), 64.7, 64.6 (CH and CH₂), 62.5 (CH), 54.0, 28.2, 25.8 (CH₃). HRMS (MH⁺) calc. for C₂₃H₂₉N₄O₅: 441.2138. Found: 441.2115.

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Example 9**Preparation of (1S)-1-(9-deazahypoxanthin-9-yl)-1,3,4-trideoxy-1,4-imino-D-ribitol hydrochloride.**

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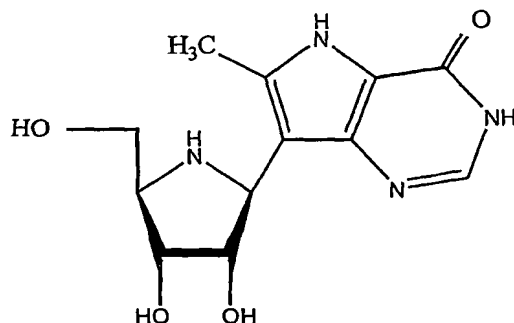
A solution of the product from example 8 (2.27 g) in THF (30 mL), water (12.5 mL) and trifluoroacetic acid (2.5 mL) was heated under reflux for 1.5 h and then concentrated to dryness. The residue in methanol (10 mL) was

treated with triethylamine (1.5 mL) and di *tert*-butyl-dicarbonate (1.67 g). After 1 h the solution was concentrated to dryness and chromatography afforded 1-(*S*)-(7-*N*-benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-D-ribitol (2.28 g). To a solution of
5 1.74 g of this material in dichloromethane (20 mL) was added diisopropylethylamine (2.4 mL), trityl chloride (1.17 g) and 4-dimethylaminopyridine (0.13 g). After 16 h at room temperature more trityl chloride (1.0 g) was added and after a further 8 h the solution was processed normally followed by chromatography to give 1-(*S*)-(7-*N*-
10 benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-5-*O*-triphenylmethyl-D-ribitol (2.27 g). Dibutyltin oxide (0.17 g) was added to a solution of 0.5 g of this material in benzene (15 mL) and the mixture was heated under reflux under a Dean Stark apparatus for 1 h. Then tetrabutylammonium bromide (0.217 g) and 4-
15 methoxybenzyl chloride (0.183 mL) were added and the solution was heated under reflux for 16 h. After concentrating to dryness chromatography of the residue afforded 1-(*S*)-(7-*N*-benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-dideoxy-1,4-imino-2-*O*-(4-methoxybenzyl)-5-*O*-triphenylmethyl-D-ribitol (0.377 g) as the major product. A solution of this
20 material in toluene (5 mL) containing thiocarbonyl diimidazole (0.148 g) was heated under reflux for 1 h. Tributyltin hydride (1 mL) was added and the solution was refluxed for a further 0.5 h. After concentrating to dryness the residue in acetonitrile was washed (x2) with petroleum ether and concentrated to dryness. Chromatography of the residue then afforded 1-
25 (*S*)-(7-*N*-benzyloxymethyl-9-deaza-6-*O*-methylhypoxanthin-9-yl)-*N*-*tert*-butoxycarbonyl-1,4-imino-2-*O*-(4-methoxybenzyl)-1,3,4-trideoxy-5-*O*-triphenylmethyl-D-ribitol (0.204 g). This material was suspended in conc. aq. HCl (5 mL) and the mixture was heated under reflux for 1 h, cooled and concentrated to dryness. Water (10 mL) was added to the residue and the
30 mixture was extracted (x2) with chloroform. The aqueous phase was concentrated to dryness and chromatography of the residue afforded a white solid which was treated with aq. HCl and lyophilised to give (1*S*)-1-(9-

deazahypoxanthin-9-yl)-1,3,4-trideoxy-1,4-imino-D-ribitol hydrochloride (0.06 g) as a white solid. ^1H NMR (D_2O) δ 7.95 (1H, s), 7.68 (1H, s), 4.95-4.84 (2H, m), 4.21 (1H, m), 3.97 (1H, dd, $J = 3.8, 12.6$ Hz), 3.83 (1H, dd, $J = 6.7, 12.6$ Hz), 2.46 (1H, m), 2.30 (1H, m); ^{13}C NMR δ 157.5, 146.0 (C), 145.3, 131.4 (CH), 120.4, 110.8 (C), 76.2, 63.8 (CH), 63.1 (CH_2), 62.7 (CH), 36.6 (CH_2). HRMS (MH) calc. for $\text{C}_{11}\text{H}_{15}\text{N}_4\text{O}_3$: 251.1144. Found: 251.1133.

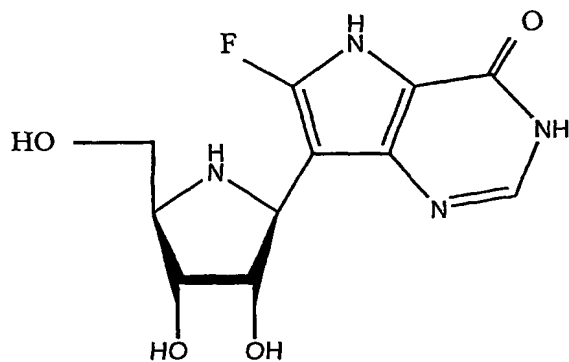
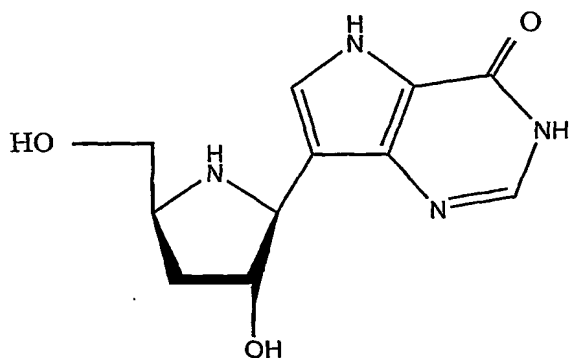
Determination of inhibition constants for bovine purine nucleoside phosphorylase

The inhibition constants for the compounds (1S)-1-(9-deaza-8-fluorohypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride, (1S)-1-(9-deaza-8-methylhypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride and (1S)-1-(9-deazahypoxanthin-9-yl)-1,3,4-trideoxy-1,4-dideoxy-1,4-imino-D-ribitol hydrochloride were determined as described in Miles et al (*Biochemistry* 37, 8615 (1998)) using bovine purine nucleoside phosphorylase (Sigma). K_i^* is the equilibrium dissociation constant for the $\text{PNP} \cdot \text{inhibitor}$ complex following slow-onset inhibition. It governs the biological properties of PNP inhibition. Not all inhibitors exhibit slow-onset binding, and others have not been experimentally examined for slow-onset inhibition. Where known, slow-onset properties are indicated. K_i and K_i^* values determined are shown below.



$K_i = 90 \text{ pM}$

2/3 partial inhibition only

 $K_i^* = 140 \text{ pM}$  $K_i = 1 \text{ nM}$

no slow onset

5

10

Although the invention has been described with reference to specific
embodiments, those persons skilled in the art will appreciate that variations
and modifications can be made without departing from the scope of the
invention.

INDUSTRIAL APPLICABILITY

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The compounds of the present invention are potent inhibitors of purine
nucleoside phosphorylase, nucleoside hydrolases and/or phosphoribosyl

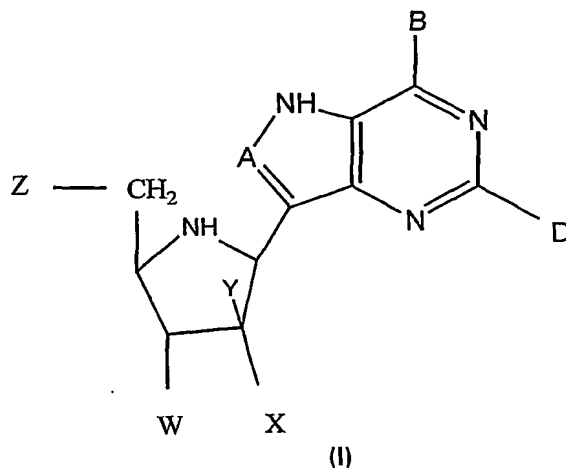
transferases. The compounds are therefore expected to have utility in treating conditions such as T-cell malignancies and autoimmune diseases. The compounds may also be useful in immunosuppression for organ transplant and inflammatory diseases.

5

In addition, the compounds of the invention are expected to be useful in the treatment and/or prophylaxis of parasitic infections, particularly those caused by protozoan parasites.

CLAIMS

1. A compound of the formula:



5 wherein:

A is selected from N, CH and CR, where R is selected from halogen, optionally substituted alkyl, aralkyl and aryl, OH, NH₂, NHR¹, NR¹R² and SR³, where R¹, R² and R³ are each optionally substituted alkyl, aralkyl or aryl groups;

10

B is selected from OH, NH₂, NHR⁴, H and halogen, where R⁴ is an optionally substituted alkyl, aralkyl or aryl group;

15 D is selected from OH, NH₂, NHR⁵, H, halogen and SCH₃, where R⁵ is an optionally substituted alkyl, aralkyl or aryl group;

X and Y are independently selected from H, OH and halogen, with the proviso that when one of X and Y is hydroxy or halogen, the other is hydrogen;

20 Z is OH, or, when X is hydroxy, Z is selected from hydrogen, halogen, hydroxy, SQ and OQ, where Q is an optionally substituted alkyl, aralkyl or aryl group; and

W is OH or H, with the proviso that when W is OH, then A is CR where R is as defined above;

or a tautomer thereof; or a pharmaceutically acceptable salt thereof; or an ester thereof; or a prodrug thereof.

2. A compound as claimed in claim 1 wherein B is NHR^4 and/or D is NHR^5 , and R^4 and/or R^5 are $\text{C}_1\text{-C}_4$ alkyl.

3. A compound as claimed in claim 1 or claim 2 wherein when one or more halogens are present, they are chosen from chlorine or fluorine.

4. A compound as claimed in any one of claims 1-3 wherein when Z is SQ or OQ, Q is $\text{C}_1\text{-C}_5$ alkyl or phenyl.

5. A compound as claimed in claim 1 wherein either D is H, or B is OH, or both.

6. A compound as claimed in claim 1 wherein B is OH, D is H, OH or NH_2 , X is OH or H and Y is H.

7. A compound as claimed in any one of claims 1-3 wherein Z is OH, H or methylthio.

8. A compound as claimed in any one of claims 1-7 wherein W is OH, Y is H, X is OH, and A is CR where R is methyl or halogen.

9. A compound as claimed in any one of claims 1-7 wherein W is H, Y is H, X is OH and A is CH.

10. A compound as claimed in claim 1 selected from

(1S)-1-(9-deaza-8-fluorohypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol;

(1S)-1-(9-deaza-8-methylhypoxanthin-9-yl)-1,4-dideoxy-1,4-imino-D-ribitol;
or
(1S)-1-(9-deazahypoxanthin-9-yl)-1,3,4-trideoxy-1,4-imino-D-ribitol;
or a tautomer thereof; or a pharmaceutically acceptable salt thereof.

5

11. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound of the formula (I) as claimed in any one of claims 1-10, and a pharmaceutically acceptable carrier or diluent.

10

12. A method for treatment of a disease or condition in which it is desirable to decrease the level of T lymphocyte activity, the method comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound as claimed in any one of claims 1-10.

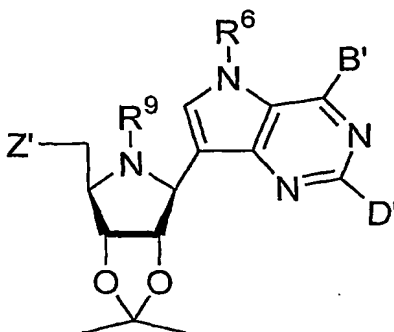
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13. A method for treatment and/or prophylaxis of a parasitic infection, the method comprising administering to a mammal in need of such treatment a pharmaceutically effective amount of a compound as claimed in any one of claims 1-10.

20

14. A method as claimed in claim 13 wherein the parasitic infection is caused by protozoan parasites.

15. A method for preparing a compound of the formula (I) as defined in claim 1, wherein A is CR and R is as defined in claim 1, the method comprising reacting



(II)

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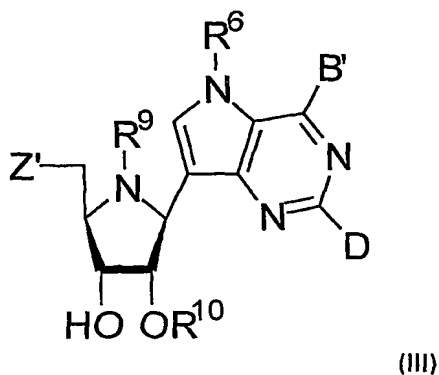
a compound of formula (II)

wherein R^9 is an alkoxycarbonyl or aralkyloxycarbonyl group, Z' is a hydrogen or halogen atom, a group of formula SQ or OQ, or a trialkylsilyloxy, alkyldiarylsilyloxy or optionally substituted triarylmethoxy group and Q is an optionally substituted alkyl, aralkyl or aryl group, and R^6 is an N-protecting group, B' and D' are independently selected from H, OR^7 and $N(R^8)_2$, and R^7 and R^8 are O- and N-protecting groups respectively;

- (i) with a strong base capable of deprotonation at C-8 of the 9-deazapurine moiety; then
- (ii) with an electrophile; and
- (iii) O- and N-deprotecting the product by acid-, alkali- or fluoride ion-catalyzed hydrolysis or alcoholysis or catalytic hydrogenolysis as required for the O- and N-protecting groups in use.

16. A method as claimed in claim 15 wherein the strong base comprises butyllithium.

17. A method for preparing a compound of the formula (I) as defined in claim 1, wherein W is H, the method comprising reacting a compound of formula (III)



- wherein R^9 is an alkoxycarbonyl or aralkyloxycarbonyl group, Z' is a hydrogen or halogen atom, a group of formula SQ or OQ, or a trialkylsilyloxy, alkyldiarylsilyloxy

or optionally substituted triarylmethoxy group and Q is an optionally substituted alkyl, aralkyl or aryl group, and R^6 is an N-protecting group, B' and D' are independently selected from H, OR^7 and $N(R^8)_2$, R^7 and R^8 are O- and N-protecting groups, respectively, and R^{10} is an O-protecting group;

5

- (i) with a thiocarbonylating agent; then
- (ii) with a radical reducing agent; and
- (iii) O- and N-deprotecting the product by acid-, alkali- or fluoride ion-catalyzed hydrolysis or alcoholysis or catalytic hydrogenolysis as required for the O- and N-protecting groups in use.

10

18. A method as claimed in claim 17 wherein the thiocarbonylating agent is thiocarbonyl diimidazole.

15

19. A method as claimed in claim 17 or claim 18 wherein the radical reducing agent comprises tributyltin hydride.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/NZ01/00174

A. CLASSIFICATION OF SUBJECT MATTERInt. Cl. ⁷: C07D 403/14; A61K 31/519; A61P 35/00, 33/02, 37/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: FILE CA Chemical Structure Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/19338 A (ALBERT EINSTEIN COLLEGE OF MEDICINE OF YESHIVA UNIVERSITY) 22 April 1999 See whole document	1-14, 18, 19
X	WO 00/61783 A (INDUSTRIAL RESEARCH LIMITED) 19 October 2000 See whole document	1-14, 18, 19
X	US 5985848 A (Richard Hubert Furneaux, et al.) 16 November 1999 See whole document	1-14, 18, 19

☒ Further documents are listed in the continuation of Box C
 ☒ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

15 October 2001

Date of mailing of the international search report 22 OCT 2001

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/NZ01/00174

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6066722 A (Richard Hubert Furneaux, et al.) 23 May 2000 See whole document	1-14, 18, 19

Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos : 15-17
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim page 26 is missing from the specification provided.
3. ☐ Claims Nos :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/NZ01/00174

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member	
WO 9919338	AU 10866/99	EP 1023308	US 5985848
	US 6066722		
WO 200061783	AU 200038469		
END OF ANNEX			